Pestic. Sci. 1998, **52**, 251–257

Synthesis and Precocious-Metamorphosis-Inducing Activity of 3-Pyridyl Ethers

Eiichi Kuwano,[1]* Motohisa Shimizu,[1] Kenshi Shimazu,[1] Satoshi Nakazawa[1] & Koichi Suzuki[2]

[1] Department of Agricultural Chemistry, Kyushu University, Higashi-ku, Fukuoka 812, Japan
[2] Faculty of Agriculture, Iwate University, Ueda, Morioka 020, Japan

(Received 14 March 1997; revised version received 1 July 1997; accepted 2 October 1997)

Abstract: A new series of 5-(substituted phenoxy)pentyl 3-pyridyl ethers induced precocious metamorphosis in larvae of the silkworm, *Bombyx mori*. Both 2- and 4-pyridyl ethers were inactive, indicating that the 3-pyridine moiety was essential for the activity. Octyl, dodecyl and farnesyl 3-pyridyl ethers had no activity. Among the compounds tested so far, 5-(4-propylphenoxy)pentyl 3-pyridyl ether showed the highest activity. The activity fell off with increasing or decreasing length of the carbon chain between two oxygen atoms. Introduction of a methyl group at the 6 position of the pyridine ring completely eliminated the activity. Precocious metamorphosis induced by 3-pyridyl ethers was fully reversible by a simultaneous application of a small amount of tebufenozide, an ecdysteroid agonist, or methoprene, a JH agonist. © 1998 SCI.

Pestic. Sci., **52**, 251–257 (1998)

Key words: *Bombyx mori*; 3-pyridyl ethers; precocious metamorphosis; tebufenozide

1 INTRODUCTION

It is well known that precocious metamorphosis is induced by allatectomy or anti-juvenile hormonal compounds.[1] We have recently reported that 1,5-disubstituted imidazoles induced precocious metamorphosis in the silkworm, *Bombyx mori* L., by causing a temporary deficiency of ecdysteroid titers in the larval hemolymph; the most effective compound, KK-42, inhibited ecdysteroid synthesis at very low concentrations *in vitro* in the prothoracic glands of the silkworm larvae.[2] Also, the ability of these imidazoles to induce precocious metamorphosis could be completely counteracted by the dietary administration of 20-hydroxyecdysone[3] or the simultaneous application of tebufenozide, an ecdysteroid agonist.[4]

In the study of the precocious-metamorphosis-inducing activity in *B. mori* larvae, we reported that the substituents at both the 1 and 5 positions of the imidazole ring were essential for the activity.[5] However, we have recently found that a number of 1-substituted imidazoles induced precocious metamorphosis in *B. mori* larvae as well.[6] This fact prompted us to examine the precocious-metamorphosis-inducing activity of pyridine derivatives because of some similar properties between the imidazole and pyridine rings (e.g. inhibitory activity for cytochrome P-450).[7] Interestingly, several pyridine derivatives have been reported to possess high juvenile hormone (JH) activity.[8] Solli *et al.*[9] first found that 3-pyridyl ethers with a terpene chain showed high JH activity, while 2- or 4-pyridyl ethers had little activity. Recently, the 2-pyridine derivative pyriproxyfen, which is very active against a wide range of insect species, has been commercialized for field applications.[10] However, there is no report in the literature of pyridine derivatives inducing precocious metamorphosis. We find that

* To whom correspondence should be addressed.
Contract/grant sponsor: Ministry of Education, Science and Culture, Japan; Contract/grant number: 07556081.

 Pestic. Sci. 0031-613X/98/$17.50. Printed in Great Britain

a new series of 3-pyridyl ethers induce precocious metamorphosis in larvae of *B. mori*. In the present paper we report their synthesis, structure and biological activity.

2 MATERIALS AND METHODS

2.1 Synthetic procedures

All melting points are uncorrected. The [^{1}H]NMR spectra were determined with a JEOL EX-400 spectrometer, using tetramethylsilane as an internal standard, and all samples were prepared in deuterochloroform.

Compounds **1–4** were synthesized according to reported methods.[9] Compounds **33** and **34** were prepared according to the procedures reported previously.[6] All (substituted phenoxy)alkyl 3-pyridyl ethers were prepared by Williamson's ether synthesis method as shown in Fig. 1. The following procedure for the preparation of 5-(4-propoxyphenoxy)pentyl-3-pyridyl ether (**21**) is typical.

2.1.1 5-(4-Propoxyphenoxy)pentyl 3-pyridyl ether (***21***)
A mixture of 4-propylphenol (1·00 g) and 1,5-dibromopentane (2·03 g) was heated to boiling. To the boiling solution was added with stirring a solution of sodium hydroxide (0·32 g) in water (8 ml) and the mixture was stirred under reflux until the solution became acidic. The product was extracted with diethyl ether, the ether solution was washed with brine, and dried over sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel by eluting with hexane + ethyl acetate (50 + 1 by volume). Concentration of the eluate under reduced pressure afforded 5-(4-propylphenoxy)pentyl bromide (1·62 g; 77·4%) as an oil. To a suspension of sodium hydride (0·15 g; 60% in oil) in dimethylformamide (10 ml) at 0–5°C was added 3-hydroxypyridine (0·33 g) and the mixture was stirred for 0·5 h at room temperature. To the ice-cooled mixture was added 5-(4-propylphenoxy)pentyl bromide (1·00 g). After stirring for 24 h at room temperature, water (50 ml) was added to the mixture, and the product was extracted with ethyl acetate. The ethyl acetate solution was washed with brine and dried over sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel by eluting with hexane + ethyl acetate (3 + 1 by volume). Concentration of the ethyl acetate eluate under reduced pressure afforded **21** (0·44 g; 41·9%), m.p. 33–34°C. [^{1}H]NMR δ: 0·92 (3H, t, J = 7·3 Hz), 1·55–1·75 (4H, m), 1·81–1·91 (4H, m), 2·52 (2H, t, J = 7·8 Hz), 3·97 (2H, t, J = 6·4 Hz), 4·03 (2H, t, J = 6·4 Hz), 6·81 (2H, d, J = 8·3 Hz), 7·07 (2H, d, J = 8·3 Hz), 7·15–7·22 (2H, m), 8·21 (1H, dd, J = 2·4 and 4·4 Hz), 8·31 (1H, d, J = 2·4 Hz). Analysis found: C, 75·99; H, 8·38; N, 4·66%. Calculated for $C_{19}H_{25}N_1O_2$: C, 76·22; H, 8·42; N, 4·68%.

Compounds **5–7** were prepared in the same manner as compound **21** with use of 3-(substituted phenoxy)propyl bromide instead of 5-(4-propylphenoxy) pentyl bromide.

2.1.2 3-(4-Phenoxyphenoxy)propyl 3-pyridyl ether (***5***)
Yield 28·1%; [^{1}H]NMR δ: 2·24–2·30 (2H, m), 4·14 (2H, t, J = 5·9 Hz), 4·21 (2H, t, J = 5·9 Hz), 6·78–7·05 (7H, m), 7·18–7·31 (4H, m), 8·19–8·22 (1H, m), 8·32–8·34 (1H, m).

2.1.3 3-Phenoxypropyl 3-pyridyl ether (***6***)
Yield 36·6%; m.p. 50–51°C; [1H]NMR δ: 2·24–2·43 (2H, m), 4·16 (2H, t, J = 5·9 Hz), 4·20 (2H, t, J = 5·9 Hz), 6·72–6·96 (3H, m), 7·19–7·29 (4H, m), 8·21 (1H, dd, J = 2·4 and 4·4 Hz), 8·31 (1H, d, J = 2·4 Hz).

2.1.4 3-(4-Ethylphenoxy)propyl-3-pyridyl ether (*7*)
Yield 58·6%; [^{1}H]NMR δ: 1·20 (3H, t, J = 7·8 Hz), 2·22–2·44 (2H, m), 2·57 (2H, q, J = 7·8 Hz), 4·12 (2H, t, J = 6·1 Hz), 4·18 (2H, t, J = 6·1 Hz), 6·83 (2H, d, J = 8·3 Hz), 7·10 (2H, d, J = 8·3 Hz), 7·17–7·25 (2H, m), 8·20 (1H, dd, J = 4·4 and 2·4 Hz), 8·32 (1H, s).

In a similar manner, compounds **8–12** were prepared by reacting 3-hydroxypyridine with the corresponding (4-ethylphenoxy)alkyl bromide.

2.1.5 2-(4-Ethylphenoxy)ethyl 3-pyridyl ether (***8***)
Yield 87·5%; m.p. 66–67°C; [^{1}H]NMR δ: 1·21 (3H, t, J = 7·8 Hz), 2·60 (2H, q, J = 7·8 Hz), 4·29–4·38 (4H, m), 6·88 (2H, d, J = 8·8 Hz), 7·12 (2H, d, J = 8·8 Hz), 7·21–7·25 (2H, m), 8·25 (1H, dd, J = 4·4 and 2·4 Hz), 8·37 (1H, d, J = 2·4 Hz).

2.1.6 4-(4-Ethylphenoxy)butyl 3-pyridyl ether (***9***)
Yield 63·5%; [^{1}H]NMR δ: 1·21 (3H, t, J = 7·8 Hz), 1·92–2·04 (4H, m), 2·58 (2H, q, J = 7·8 Hz), 4·01 (2H, t, J = 5·9 Hz), 4·07 (2H, t, J = 5·9 Hz), 6·82 (2H, d, J = 8·8 Hz), 7·10 (2H, d, J = 8·8 Hz), 7·17–7·19 (2H, m), 8·21 (1H, dd, J = 4·4 and 2·4 Hz), 8·31 (1H, d, J = 2·4 Hz).

2.1.7 5-(4-Ethylphenoxy)pentyl 3-pyridyl ether (***10***)
Yield 38·0%; m.p. 28–29°C; [^{1}H]NMR δ: 1·21 (3H, t, J = 7·8 Hz), 1·64–1·69 (2H, m), 1·85–1·89 (4H, m), 2·53–

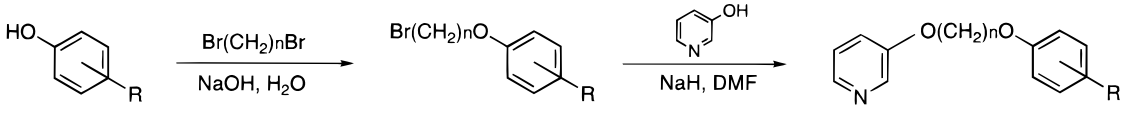


Fig. 1. Synthetic scheme for preparation of (substituted phenoxy)alkyl 3-pyridyl ethers.

2·61 (2H, m), 3·95–4·14 (4H, m), 6·81–6·86 (2H, m), 7·09–7·14 (2H, m), 7·15–7·26 (2H, m), 8·21 (1H, dd, J = 2·4 and 4·4 Hz), 8·31–8·33 (1H, m).

2.1.8 6-(4-Ethylphenoxy)hexyl 3-pyridyl ether (***11***)
Yield 31·8%; m.p. 50–51°C; [^{1}H]NMR δ: 1·20 (3H, t, J = 7·8 Hz), 1·50–1·55 (4H, m), 1·71–1·94 (4H, m), 2·57 (2H, q, J = 7·8 Hz), 3·94 (2H, t, J = 6·4 Hz), 3·99 (2H, t, J = 6·4 Hz), 6·81 (2H, d, J = 8·8 Hz), 7·09 (2H, d, J = 8·8 Hz), 7·13–7·19 (2H, m), 8·19 (1H, dd, J = 2·4 and 4·4 Hz), 8·30 (1H, d, *J* = 2·4 Hz).

2.1.9 7-(4-Ethylphenoxy)heptyl 3-pyridyl ether (***12***)
Yield 33·8%; [^{1}H]NMR δ: 1·20 (3H, t, J = 7·8 Hz), 1·39–1·54 (6H, m), 1·75–1·84 (4H, m), 2·58 (2H, q, J = 7·8 Hz), 3·93 (2H, t, J = 6·4 Hz), 3·99 (2H, t, J = 6·4 Hz), 6·81 (2H, d, J = 8·8 Hz), 7·09 (2H, d, J = 8·8 Hz), 7·13–7·19 (2H, m), 8·19 (1H, dd, J = 2·4 and 4·4 Hz), 8·30 (1H, d, J = 2·4 Hz).

Compounds **13**–**20** and **22**–**28** were prepared in the same manner as that used for compound **21** from the corresponding 5-(substituted phenoxy)pentyl bromide and 3-hydroxypyridine.

2.1.10 5-Phenoxypentyl 3-pyridyl ether (***13***)
Yield 8·6%; [^{1}H]NMR δ: 1·60–1·68 (2H, m), 1·80–1·89 (4H, m), 3·92–4·00 (4H, m), 6·87–6·93 (3H, m), 7·13–7·30 (4H, m), 8·16–8·22 (1H, m), 8·30–8·32 (1H, m).

2.1.11 5-(4-Chlorophenoxy)pentyl 3-pyridyl ether (***14***)
Yield 28·8%; m.p. 45–46°C; [^{1}H]NMR δ: 1·53–1·60 (2H, m), 1·70–1·85 (4H, m), 3·86 (2H, t, J = 6·4 Hz), 3·93 (2H, t, J = 6·4 Hz), 6·71–6·74 (2H, m), 7·06–7·15 (4H, m), 8·11–8·12 (1H, m), 8·22–8·23 (1H, m).

2.1.12 5-(3-Chlorophenoxy)pentyl 3-pyridyl ether (***15***)
Yield 37·6%; [^{1}H]NMR δ: 1·58–1·65 (2H, m), 1·78–1·87 (4H, m), 3·94 (2H, t, J = 6·4 Hz), 3·97 (2H, t, J = 6·4 Hz), 6·74–6·76 (1H, m), 6·86–6·88 (2H, m), 7·12–7·18 (3H, m), 8·17–8·18 (1H, m), 8·28 (1H, s).

2.1.13 5-(2-Chlorophenoxy)pentyl 3-pyridyl ether (***16***)
Yield 38·1%; [^{1}H]NMR δ: 1·62–1·70 (2H, m), 1·78–1·94 (4H, m), 3·98 (2H, t, J = 6·4 Hz), 4·00 (2H, t, J = 6·4 Hz), 6·81–6·88 (2H, m), 7·11–7·17 (3H, m), 7·30–7·32 (1H, m), 8·16 (1H, s), 8·28 (1H, s).

2.1.14 5-(2,4-Dichlorophenoxy)pentyl 3-pyridyl ether (***17***)
Yield 35·9%; [^{1}H]NMR δ: 1·58–1·66 (2H, m), 1·78–1·86 (4H, m), 3·94 (2H, t, J = 6·4 Hz), 3·97 (2H, t, J = 6·4 Hz), 6·74 (1H, d, J = 8·8 Hz), 7·06–7·14 (3H, m), 7·26 (1H, d, J = 2·4 Hz), 8·13 (1H, dd, J = 2·0 and 4·4 Hz), 8·23 (1H, J = 2·0 Hz).

2.1.15 5-(4-Bromophenoxy)pentyl 3-pyridyl ether (**18**)
Yield 65·1%; [^{1}H]NMR δ: 1·63–1·69 (2H, m), 1·82–1·91 (4H, m), 3·96 (2H, t, J = 6·4 Hz), 4·03 (2H, t, J = 6·4 Hz), 6·77 (2H, d, J = 9·3 Hz), 7·16–7·22 (2H, m), 7·35 (2H, d, J = 9·3 Hz), 7·35 (1H, dd, J = 2·4 and 4·4 Hz), 8·30 (1H, d, J = 2·4 Hz).

2.1.16 5-(4-(Fluorophenoxy) pentyl 3-pyridyl ether (***19***)
Yield 43·6%; [^{1}H]NMR δ: 1·57–1·65 (2H, m), 1·77–1·86 (4H, m), 3·89 (2H, t, J = 6·4 Hz), 3·97 (2H, t, J = 6·4 Hz), 6·73–6·82 (2H, m), 6·85–6·96 (2H, m), 7·09–7·17 (2H, m), 8·20–8·26 (1H, m), 8·27–8·30 (1H, m).

2.1.17 5-(4-Methylphenoxy)pentyl 3-pyridyl ether (***20***)
Yield 41·7%; m.p. 46–47°C; [^{1}H]NMR δ: 1·62–1·70 (2H, m), 1·81–1·92 (4H, m), 2·28 (3H, s), 3·97 (2H, t, J = 6·4 Hz), 4·01 (2H, t, J = 6·4 Hz), 6·80 (2H, d, J = 8·3 Hz), 7·07 (2H, d, J = 8·3 Hz), 7·16–7·22 (2H, m), 8·21 (1H, dd, J = 2·4 and 4·4 Hz), 8·31 (1H, d, J = 2·4 Hz).

2.1.18 5-(4-Isopropylphenoxy)pentyl 3-pyridyl ether (***22***)
Yield 20·8%; [^{1}H]NMR δ: 1·14 (6H, d, J = 6·8 Hz), 1·55–1·61 (2H, m), 1·75–1·84 (4H, m), 2·75–2·80 (1H, m), 3·89 (2H, t, J = 6·4 Hz), 3·95 (2H, t, J = 6·4 Hz), 6·70–6·77 (4H, m), 7·06 (2H, d, J = 8·3 Hz), 8·33–8·34 (2H, m).

2.1.19 5-(4-t-Butylphenoxy)pentyl 3-pyridyl ether (***23***)
Yield 23·5%; [^{1}H]NMR δ: 1·29 (9H, s), 1·65–1·67 (2H, m), 1·83—1·88 (4H, m), 3·97 (2H, t, J = 6·4 Hz), 4·02 (2H, t, J = 6·4 Hz), 6·82–6·84 (2H, m), 7·17–7·30 (6H, m), 8·19–8·20 (1H, m), 8·30–8·31 (1H, m).

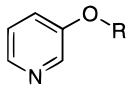
2.1.20 5-(4-Methoxyphenoxy)pentyl ether (***24***)
Yield 38·7%; [^{1}H]NMR δ: 1·57–1·67 (2H, m), 1·74–1·84 (4H, m), 3·71 (3H, s), 3·89 (2H, t, J = 6·4 Hz), 3·97 (2H, t, J = 6·4 Hz), 6·79 (4H, s), 7·11–7·16 (2H, m), 8·16 (1H, dd, J = 2·4 and 4·4 Hz), 8·27 (1H, d, J = 2·4 Hz).

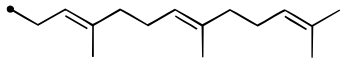
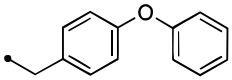
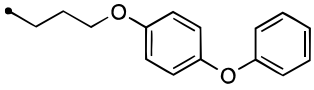
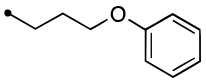
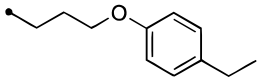
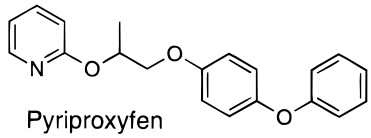
2.1.21 5-(4-Ethoxyphenoxy)pentyl 3-pyridyl ether (***25***)
Yield 20·4%; [^{1}H]NMR δ: 1·38 (3H, t, J = 6·8 Hz), 1·63–1·69 (2H, m), 1·79–1·91 (4H, m), 3·92–4·04 (6H, m), 6·80–6·84 (4H, m), 7·17–7·26 (2H, m), 8·19–8·21 (1H, m), 8·30–8·31 (1H, m).

2.1.22 5-(4-Propoxyphenoxy)pentyl 3-pyridyl ether (***26***)
Yield 24·6%; m.p. 48–49°C; [^{1}H]NMR δ: 1·01 (3H, t, J = 7·3 Hz), 1·61–1·69 (2H, m), 1·75–1·89 (6H, m), 3·86 (2H, t, J = 6·4 Hz), 3·93 (2H, t, J = 6·4 Hz), 4·02 (2H, t, J = 6·4 Hz), 6·80–6·84 (4H, m), 7·17–7·20 (2H, m), 8·19–8·21 (1H, m), 8·30–8·31 (1H, m).

2.1.23 5-(4-Phenoxyphenoxy)pentyl 3-pyridyl ether (***27***)
Yield 45·8%; [^{1}H]NMR δ: 1·63–1·95 (6H, m), 4·13 (2H, t, J = 6·4 Hz), 4·20 (2H, t, J = 6·4 Hz), 6·86–7·05 (7H,

TABLE 1
Precocious-Metamorphosis-Inducing Activity of 3-Pyridyl Ethers and Pyriproxyfen against the 4th-instar Larvae of *Bombyx mori*



No.	*R*	*Activity* (%) *Dose* (*160 μg per larva*)
1	*n*-C_8H_{17}	0
2	*n*-$C_{12}H_{25}$	0
3		0
4		0
5		0
6		20
7		30
	 Pyriproxyfen	0

m), 7·17–7·30 (4H, m), 8·20–8·22 (1H, m), 8·32–8·33 (1H, m).

2.1.24 5-(4-Benzyloxyphenoxy)pentyl 3-pyridyl ether (***28***)
Yield 24·0%; m.p. 46–47°C; [^{1}H]NMR δ: 1·62–1·71 (2H, m), 1·83–1·94 (4H, m), 3·91 (2H, t, J = 6·3 Hz), 4·13 (2H, t, J = 6·3 Hz), 5·02 (2H, s), 6·82–6·84 (2H, m), 6·88–6·92 (2H, m), 7·15–7·22 (2H, m), 7·29–7·43 (5H, m), 8·20 (1H, dd, J = 2·4 and 4·4 Hz), 8·31 (1H, d, J = 2·4 Hz).

Compounds **29**–**32** were prepared in the same manner as **21** with use of 2-hydroxypyridine, 4-hydroxypyridine, 5-hydroxy-2-methylpyridine and phenol respectively, instead of 3-hydroxypyridine.

2.1.25 5-(4-Propylphenoxy)pentyl 2-pyridyl ether (***29***)
Yield 22·5%; [^{1}H]NMR δ: 0·91 (3H, t, J = 7·3 Hz), 1·48–1·64 (4H, m), 1·77–1·88 (4H, m), 2·51 (2H, t, J = 7·3 Hz), 3·91–3·96 (4H, m), 6·11–6·15 (1H, m), 6·54–6·80 (1H, m), 7·06 (2H, d, J = 8·8 Hz), 7·22–7·32 (4H, m).

2.1.26 5-(4-Propylphenoxy)pentyl 4-pyridyl ether (***30***)
Yield 17·5%, [^{1}H]NMR δ: 0·84 (3H, t, J = 7·3 Hz), 1·47–1·60 (4H, m), 1·73–1·82 (4H, m), 2·43 (2H, t, J = 7·3 Hz), 3·88 (2H, t, J = 6·4 Hz), 3·93 (2H, t, J = 6·4 Hz), 6·69–6·74 (4H, m), 6·99 (2H, d, J = 8·3 Hz), 8·32–8·33 (2H, m).

2.1.27 5-(4-Propylphenoxy)pentyl 2-methyl-5-pyridyl ether (***31***)
Yield 18·8%; [^{1}H]NMR δ: 0·92 (3H, t, J = 7·3 Hz), 1·54–1·64 (4H, m), 1·76–1·97 (4H, m), 2·48 (3H, s), 2·51 (2H, t, J = 7·8 Hz), 3·97 (2H, t, J = 6·4 Hz), 3·99 (2H, t, J = 6·4 Hz), 6·86 (2H, d, J = 8·8 Hz), 6·93–7·08 (4H, m), 8·18 (1H, s).

2.1.28 Phenyl 5-(4-propylphenoxy)pentyl ether (***32***)
Yield 82·2%; [^{1}H]NMR δ: 0·92 (3H, t, J = 7·3 Hz) 1·55–1·67 (4H, m), 1·80–1·86 (4H, m), 2·51 (2H, t, J = 7·8 Hz), 3·93–3·98 (4H, m), 6·80 (2H, d, J = 8·3 Hz), 6·87–6·94 (3H, m), 7·06 (2H, d, J = 8·3 Hz), 7·20–7·28 (2H, m).

2.2 Biological evaluations

B. mori (Shunrei × Shougetsu strain) larvae were reared on artificial diets as previously described.[3] The pyridine

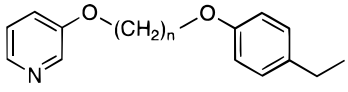
compounds, methoprene and tebufenozide in acetone solution (1–4 μl per larva) were applied topically to newly molted 4th-instar larvae and 24-h-old 3rd-instar larvae. The activity was evaluated in terms of induction of precocious metamorphosis as described by Kuwano *et al.*[11]: spinning a cocoon and subsequent pupation from the 4th-instar (penultimate) larval period. The precocious pupae caused by applying pyridine compounds molted to miniature adults.

3 RESULTS AND DISCUSSION

Since 1-decyl- or 1-dodecylimidazole induced precocious metamorphosis in the 4th-instar larvae of the silkworm,[6] we first synthesized several alkyl 3-pyridyl ethers and evaluated their activity (Table 1). In contrast to 1-substituted imidazoles, simple alkyl 3-pyridyl ethers such as octyl (**1**) or dodecyl (**2**) ether showed insecticidal activity in *B. mori* larvae and did not induce precocious metamorphosis. Farnesyl 3-pyridyl ether (**3**), which has a similar structure to pyridyl terpenoid ether with high JH activity,[8] did not induce precocious metamorphosis even at a high dose of 160 μg per larva. Compounds **4** and **5**, with a phenoxyphenyl substituent, showing similarity to some JH mimics, had no activity at 160 μg per larva, either. Pyriproxyfen showed no activity against the 4th-instar larvae of silkworm except for a slight prolongation of the 4th-instar period. Only 3-phenoxypropyl 3-pyridyl ether (**6**) and its 3-(4-ethylphenoxy)propyl analog (**7**) induced precocious metamorphosis in the silkworm, and thus a modification was made by replacing the propyl group of the compound **7** with other alkyl groups (Table 2). Among a series of (4-ethylphenoxy)alkyl 3-pyridyl ethers, the 5-(4-ethylphenoxy)pentyl analog (**10**) showed the highest activity. The activity decreased with increasing or decreasing length of the carbon chain between the two oxygen atoms. Interestingly, the compounds with an even-number alkyl chain had little precocious-metamorphosis-inducing activity.

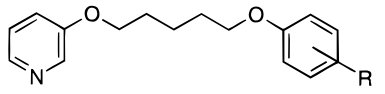
Table 3 lists the ED_{50} values of some 5-phenoxypentyl 3-pyridyl ether analogs with different substituents on the benzene ring. The unsubstituted phenyl compound (**13**) did not induce precocious metamorphosis at 160 μg per larva. The introduction of a chloro substituent at the *para* position on the benzene ring (compound **14**) increased the activity in comparison with that of compound **10**, while the 3- and 2-chlorophenyl analogs (**15** and **16**) gave much lower activity. 2,4-Dichloro and 4-bromophenyl analogs (**17** and **18**) had almost the same activity as that of compound **10**, whereas the 4-fluorophenyl analog (**19**) showed much lower activity. The 4-propylphenyl analog (**21**) was twice as active as the 4-ethylphenyl analog (**10**), while the 4-isopropylphenyl analog (**22**) showed very low activity in comparison with the activity observed for compound **21**. The 4-*tert*-butylphenyl analog (**23**) was inactive at 160 μg per larva, indicating that the size of the alkyl substituent on the benzene ring plays an important role for activity. The 4-ethoxyphenyl analog (**25**) showed higher activity than compound **10**, while the 4-methoxy- and 4-propoxyphenyl analogs (**24** and **26**) had considerably lower activity. The introduction of a phenoxy or benzyloxy group into the benzene ring (**27** and **28**) completely eliminated the activity at 160 μg per larva. Among the compounds tested so far, 5-(4-propylphenoxy)pentyl 3-pyridyl ether (**21**) was the most

TABLE 2
Precocious-Metamorphosis-Inducing Activity of (4-Ethylphenoxy)alkyl 3-Pyridyl Ethers against the 4th-Instar Larvae of *Bombyx mori*



No.	n	*Activity* (%) *Dose 160* (*μg per larva*)
8	2	0
7	3	30
9	4	0
10	5	70
11	6	0
12	7	30

TABLE 3
Precocious-Metamorphosis-Inducing Activity of 5-(Substituted Phenoxy)pentyl 3-Pyridyl Ethers against the 4th-instar Larvae of *Bombyx mori*



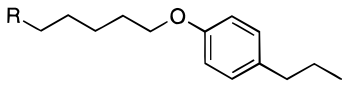
No.	*R*	ED_{50} (*μg per larva*)[a]
13	H	>160 (0)
14	4-Cl	40
15	3-Cl	>160 (0)
16	2-Cl	>160 (10)
17	2,4-Cl_2	61
18	4-Br	71
19	4-F	>160 (20)
20	4-CH_3	>80 (40)
10	4-C_2H_5	67
21	4-*n*-C_3H_7	32
22	4-*i*-C_3H_7	>80 (10)
23	4-*t*-C_4H_9	>160 (0)
24	4-OCH_3	>160 (10)
25	4-OC_2H_5	43
26	4-O-*n*-C_3H_7	>160 (30)
27	4-OC_6H_5	>160 (0)
28	4-$OCH_2C_6H_5$	>160 (0)

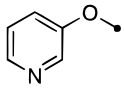
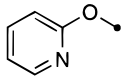
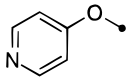
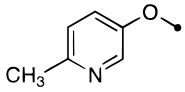
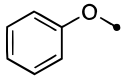
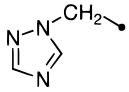
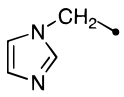
[a] Numbers in parentheses show percentage precocious pupation at specified doses.

effective of the analogs tested on the 4th-instar larvae of *B. mori*.

For the 5-(4-propylphenoxy)pentyl 3-pyridyl ether (**21**), replacement of the 3-pyridyl group by a 2-pyridyl (**29**), 4-pyridyl (**30**) or phenyl (**32**) group gave analogs with negligible precocious-metamorphosis-inducing activity (Table 4). This result indicates that the presence of a 3-pyridyl group is essential for activity. In contrast to the results found in 3-pyridyl terpenoid ethers with JH activity,[9] the introduction of a methyl group on the 6-position of the pyridine ring (**31**) led to a drastic decrease in precocious-metamorphosis-inducing activity. It is noteworthy that 1-[5-(4-propylphenoxy)hexyl] imidazole (**34**) showed activity comparable to that of compound **21**, whereas the 1,2,4-triazole derivative with the same substituent (**33**) did not induce precocious metamorphosis even at a high dose of 160 μg per larva.

TABLE 4
Precocious-Metamorphosis-Inducing Activity of Pyridyl Ethers and Related Compounds against the 4th-instar Larvae of *Bombyx mori*



No.	*R*	ED_{50} (*μg per larva*)[a]
21		32
29		>160 (0)
30		>160 (0)
31		>160 (0)
32		>160 (0)
33		>160 (0)
34		34

[a] Numbers in parentheses show percentage precocious pupation at specified doses.

It has been reported that a variety of 1,5-disubstituted imidazoles showed precocious-metamorphosis-inducing activity against 3rd-instar larvae as well as against 4th-instar larvae. Table 5 shows the effect of representative compounds **14** and **21** on 24-h-old 3rd-instar larvae of *B. mori*. Third-instar larvae were less sensitive than 4th-instar larvae to the 3-pyridyl ethers. Compounds **14** showed no activity even at a dose of 160 μg per larva, while compound **21** induced precocious metamorphosis against 3rd-instar larvae, though the activity was weak. In this case, precocious metamorphosis occurred in the 4th (penultimate) larval stage. None of the treated 3rd-instar larvae metamorphosed into precocious pupae in the same larval stage by a single topical application of compound **21**, which is similar to the effect of 1,5-disubstituted imidazoles.

In the 4th-instar larvae, precocious metamorphosis induced by compounds **14** and **21** was completely prevented not only by a simultaneous application of 10 μg of methoprene, a JH mimic, but also by 0·01 μg of tebufenozide, an ecdysteroid agonist (Table 6). The latter result suggests that these 3-pyridyl ethers, as well as 1,5-disubstituted imidazoles and 1-substituted imidazoles, temporarily depress the ecdysteroid titer in the larval

TABLE 5
Precocious-Metamorphosis-Inducing Activity of 3-Pyridyl Ethers against 24-h-old 3rd-instar Larvae

Compound	*Dose* (*μg per larva*)	*Activity* (%)
14	20	0
14	40	0
14	80	0
14	160	0
21	20	0
21	40	10
21	80	15
21	160	40

TABLE 6
Effects of Methoprene and Tebufenozide on Precocious Metamorphosis Induced by 3-Pyridyl Ethers against the 4th-instar Larvae of *Bombyx mori*

Compound No.	*Dose* (*μg per larva*)	*Precocious metamorphosis* (%)		
		Alone	*+Methoprene* (*10 μg*)	*+Tebufenozide* (*0·01 μg*)
14	80	65	0	0
21	80	80	0	0

hemolymph to induce precocious metamorphosis. However, counteraction by methoprene suggests some interaction with JH biosynthesis or action as well. On the basis of the preliminary biological data described in this article, it is concluded that 3-pyridyl ethers represent reasonable leads for the development of new insect growth regulators.

ACKNOWLEDGEMENT

We thank Prof. Lawrence G. Harshman of University of Nebraska for his critical reading and improvement of this manuscript. This work was supported in part by grant-aid for scientific research (No. 07556081) from the Ministry of Education, Science and Culture of Japan.

REFERENCES

1. Staal, G. B., Antijuvenile hormone agents. *Ann. Rev. Entomol.*, **31** (1986) 391–429.
2. Yamashita, O., Kadono-Okuda, K., Kuwano, E. & Eto, M., An imidazole compound as a potent anti-ecdysteroid in an insect. *Agric. Biol. Chem.*, **51** (1987) 2295–7.
3. Kuwano, E., Hisano, T., Sonoda, M. & Eto, M., Effects of methoprene and 20-hydroxyecdysone on the precocious metamorphosis induced by 1,5-disubstituted imidazoles. *Biosci. Biotech. Biochem.*, **58** (1994) 1309–10.
4. Sonoda, M., Kuwano, E. & Taniguchi, E., Precocious metamorphosis induced by 1,5-disubstituted imidazoles is counteracted by tebufenozide (RH-5992), an ecdysteroid agonist. *Nihon Noyaku Gakkaishi* (*J. Pestic. Sci.*), **20** (1995) 325–7.
5. Kuwano, E., Takeya, R. & Eto, M., Terpenoid imidazoles: New anti-juvenile hormones. *Agric. Biol. Chem.*, **47** (1983) 921–3.
6. Shimazu, K., Shimizu, M., Suzuki, K. & Kuwano, E., Precocious-metamorphosis-inducing activity of 1-substituted imidazoles. *Nihon Noyaku Gakkaishi* (*J. Pestic. Sci.*), **21** (1996) 337–9.
7. Ortiz de Montellano, P. R. & Reich, N. O., In *Cytochrome P-450*, ed. P. R. Ortiz de Montellano. Plenum, New York, 1986, pp. 273–314.
8. Kramer, K. J., McGregor, H. E. & Mori, K., Susceptibility of stored-product insects to pyridyl ether analogues of juvenile hormone. *J. Agric. Food Chem.*, **27** (1979) 1215–17.
9. Solli, H., Madsen, H. B., Holst, P. L. & Klemmensen P. D., Pyridyl terpenoid ethers with high juvenile hormone activity. *Pestic. Sci.*, **7** (1976) 503–11.
10. Henrick, C. A., In *Agrochemicals From Natural Products*, ed. C. R. A. Godfrey. Marcel Dekker, New York, 1995, pp. 147–213.
11. Kuwano, E., Hisano, T. & Eto, M., Synthesis and insect growth regulatory activity of 1,5-disubstituted imidazoles with non-terpene chains. *Agric. Biol. Chem.*, **55** (1991) 2999–3004.